Ovarian conservation vs removal at the time of benign hysterectomy

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Over the last 2 decades, the rate of oophorectomy at the time of hysterectomy in the United States has consistently been between 40-50%. A decline in hormone use has been observed since the release of the principal results of the Women's Health Initiative. Oophorectomy appears to be associated with an increased risk of coronary heart disease, as well as deleterious effects on overall mortality, cognitive functioning, and sexual functioning. Estrogen deficiency from surgical menopause is associated with bone mineral density loss and increased fracture risk. While hormone therapy may mitigate these effects, at no age does there appear to be a survival benefit associated with oophorectomy. Reduction of ovarian cancer risk may be accomplished with salpingectomy at the time of hysterectomy.

Key words: morbidity, mortality, oophorectomy, ovarian cancer, ovarian conservation

Introduction

Oophorectomy at the time of hysterectomy occurs at a rate of 40-50% in the United States.[1-5] Commonly cited rationales for bilateral salpingo-oophorectomy (BSO) are prevention of ovarian cancer and decreased risk of subsequent surgery. The sequelae of BSO include increased mortality due to all causes, cardiovascular disease, deficits of cognitive and sexual functioning, and osteoporosis. Historically, hormone therapy (HT) has been used to mitigate the effects of estrogen deficiency. In a study of HT compliance, 3% of women discontinued HT by 2 years, 20% by 5 years, and 67% by 10 years.[6] The Women's Health Initiative (WHI) observed a discontinuation rate of 42% at an average of 5.2 years of follow-up.[7] Although the primary objective of the WHI was to evaluate whether HT had favorable effects on coronary heart disease (CHD),[7,8] its main effect was to change the prescribing practice of HT.

Importantly, the postmenopausal ovary appears to be an ongoing site of testosterone production. A decline in serum androgens is observed throughout the reproductive years, with minimal change in the midlife, and a slight increase in the seventh decade. While natural menopause does not seem to affect serum androgen levels, oophorectomy results in significantly lower levels of total and free testosterone.[9] The postmenopausal ovary is therefore a source of androgens in older women, and provides precursors for estrogen metabolism. This is particularly relevant to bone health, cardiovascular health, sexual functioning, and cognitive functioning. In this article, we consider recent trends in oophorectomy, the risks and benefits, the role of HT, and alternatives for risk reduction of ovarian cancer.

Trends in oophorectomy

Multiple large population-based databases have examined the overall rate of oophorectomy at the time of hysterectomy in the United States. The percentage has been consistently in the mid-40s (43.7%-46.7%).[1-5] After the release of the initial WHI results in 2002, an acute decline in BSO rate was noted.[3,4,10] The decline was observed in all age groups, but most notably in women aged 45-49 years.[10] While the age-adjusted risk of oophorectomy with hysterectomy declined in women ≤50 years of age, the risk for women age >50 years increased.[11]

Age has repeatedly been identified as an independent risk factor for elective oophorectomy during hysterectomy, starting as young as 45 years. Lowder et al[11] observed an odds ratio of 11.4 (95% confidence interval [CI], 10.2−12.7) for oophorectomy at age 45-49 years, and 17.7 (95% CI, 15.6−20.2) at age 50-54 years, when compared to women <35 years old. Similarly, Asante et al[10] observed the highest rates of elective oophorectomy in women aged 45-49 years, followed by women aged 50-54 years. In a study by Jacoby et al,[1] the odds of undergoing BSO increased approximately 30% with each year of advancing age between 40-49 years. Despite the recent increase in ovarian conservation for women aged 45-49 years, the rate of oophorectomy in this age group is approximately 60%.[1,5] The rate of oophorectomy in women age of >55 years is 65-75%.[1,3,5]

While age appears to play the most prominent role in the decision to remove or retain ovaries, several clinical and demographic variables have also been identified. A personal history of breast cancer or a family history of breast or ovarian cancer is associated with elective oophorectomy during hysterectomy, even when genetic susceptibility mutations are not identified.[2,4]

All-cause mortality

In 2005, Parker et al[12] published a Markov decision analysis to estimate the optimal strategy for maximizing survival in women at average risk of ovarian cancer. The risks and benefits of

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TABLE 1
All-cause mortality and oophorectomy

Author	Cohort	Deleterious effect of BSO	Major findings
Ossewaard et al,[13] 2005	Dutch breast cancer screening cohort	Yes	• 2% Decrease in total mortality per year of delayed menopause
Rocca et al,[14] 2006	Mayo Clinic Cohort Study of Oophorectomy and Aging	Yes	• Increased risk of mortality with bilateral oophorectomy age <45 y (HR, 1.67; 95% CI, 1.16–2.40)
Parker et al,[15] 2009 Parker et al,[16] 2013	Nurses' Health Study	Yes	• Oophorectomy associated with increased risk of all-cause death (HR, 1.13; 95% CI, 1.06–1.21) • Even higher risk of all-cause death observed in women who underwent oophorectomy age <50 y, and never used estrogen therapy (HR, 1.41; 95% CI, 1.04–1.92)
Jacoby et al,[19] 2011	Women's Health Initiative	No	• BSO not associated with increased risk of death in multivariate analysis (HR, 0.98; 95% CI, 0.87–1.10) • BSO not associated with increased risk of death in subset of women who never used HT (HR, 0.99; 95% CI, 0.80–1.23)
Gierach et al,[17] 2014	Breast Cancer Detection Demonstration Project	Yes	• Women who underwent BSO by age 35 y had increased risk of death from any cause (HR, 1.20; 95% CI, 1.08–1.34), which progressively decreased when surgery was performed later in life • By age 50 y, risk was no longer increased (HR, 1.05; 95% CI, 0.99–1.10)
Mytton et al,[18] 2017	English Healthcare Registries	Yes	• Ovarian conservation was associated with significantly lower rate of all-cause death (HR, 0.64; 95% CI, 0.55–0.73)

BSO, bilateral salpingo-oophorectomy; *CI*, confidence interval; *HR*, hazard ratio; *HT*, hormone therapy.

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oophorectomy at the time of surgery for benign gynecologic disease were considered, and included overall mortality, as well as mortality from CHD, hip fracture, stroke, ovarian cancer, and breast cancer. The highest rates of survival were observed in the ovarian conservation cohorts, either with or without estrogen therapy (ET), and were measured in survival to age 80 years. Oophorectomy with ET was associated with a comparable survival (62.15%) to ovarian conservation with ET (62.75%), while oophorectomy without ET was associated with a much lower proportion of survival (53.88%).

Similar results have been observed in a variety of large cohort studies (Table 1), including a Dutch breast cancer screening cohort,[13] the Mayo Clinic Cohort Study of Oophorectomy and Aging,[14] the Nurses' Health Study,[15,16] the Breast Cancer Detection Demonstration Project,[17] as well as a retrospective analysis of English national databases.[18] An increased risk of death from any cause was particularly apparent in women who underwent oophorectomy age <45-50 years, and never used ET. At no age was there an overall survival benefit associated with bilateral oophorectomy at the time of hysterectomy.

The only large prospective observational cohort to not demonstrate a deleterious effect of BSO on mortality was the WHI.[19] In multivariate analysis, BSO was not associated with an increased risk of overall mortality. However, the differences in study demographics should be taken into consideration when this cohort is used for comparison. The average age at the time of enrollment was 63 years, average follow-up was 7.6 years, and 78.6% of the cohort were past or current users of HT. The relatively older age at the time of enrollment, shorter follow-up, and prevalence of HT use may account for the absence of any interaction between BSO and mortality that was observed in the other studies.

In summary, the vast majority of the literature supports a deleterious effect of oophorectomy on overall mortality, particularly when performed at age <50 years. ET appears to mitigate the increase in overall mortality associated with oophorectomy, but at no age was a survival benefit shown. Based on Markov modeling, ovarian conservation may even confer a long-term survival benefit until the age of 65 years.[12]

Cancer risk and mortality

It has been estimated that 1000 cases of ovarian cancer could be prevented annually, if every woman age >40 years underwent BSO at the time of